43. The method according to claim 39 wherein the matrix is in the form of sheets, gels, filters, membranes, fibres, tubes, microtitre plates, columns, particles.

44. The method according to claim 43 wherein the matrix is a porous material.

45. The method according to claim 44 wherein the matrix is incorporated into a separation device selected from centrifuge vials, microtiter plates, cartridges and syringes.

46. The method according to claim 43 wherein an absorbent pad is located on said porous material, a liquid impermeable sheet is located on the face of said absorbent pad remote from said porous material, and a liquid impermeable sheet having one or more holes therein is located on the face of said porous material remote from said absorbent pad, whereby the test sample is applied to one of said holes and is caused to diffuse transversely through said porous material by absorption into said absorbent pad.

47. The method according to claim 39 for the at least partial separation of a product of restriction enzyme digestion, or for purifying the products of the PCR reaction.

48. The method according to claim 39 for at least partially separating a mixture of restriction enzyme digested fragments of DNA wherein the starting material is a linear DNA molecule which is tagged or capable of being tagged at or near one or both ends with a moiety capable of being immobilised on a matrix, said method comprising subjecting the DNA molecule to restriction enzyme digestion followed by contacting the sample with a matrix whereby the tagged molecules which originate from an end of the starting material are captured by the matrix and are thereby separated from untagged molecules.

49. The method according to claim 39 for at least partially separating the correct and desired products of PCR amplification from PCR products which result from incorrect annealing of a PCR primer to template, wherein the template nucleic acid molecule comprises a unique restriction enzyme recognition site at or towards an end of the template, and a PCR primer which is tagged or capable of being tagged is complementary to a sequence

on the template which extends partially into the unique restriction site, the method comprising amplifying the template by means of PCR, digesting the PCR products with the restriction enzyme specific for the said unique restriction enzyme recognition site, and contacting the resulting product with a matrix capable of sequestering the tag whereby tagged nucleic acid molecules are captured by the matrix and thereby separated from untagged molecules.

50. The method according to claim 49 wherein the tag is attached at the 5' end of the primer.

51. The method according to claim 39 wherein said nucleic acids are further amplified by polymerase chain reaction.

52. The method according to claim 51 wherein a test sample is separately subjected to PCR reactions, in which the mutation, if present, is in the sequence to which the 3' primer is complementary, a first PCR reaction using a 3' primer complementary to the normal target nucleic acid and a second PCR reaction using a 3' primer complementary to the mutant target, wherein the 3' nucleotide of the mutant primer corresponds to one of the nucleotides which is mutated in the mutant nucleic acid, each of said 3' primers bearing a tag or being capable of being tagged on the 3' nucleotide of the primer, wherein the presence or absence of the tag in the PCR reaction products is detected.

53. The method according to claim 51 wherein the presence or absence of a mutation in a nucleic acid sample is detected, wherein a 3' primer specific for either the normal or mutant nucleic acid is used, wherein said primer is complementary to a region of the nucleic acid where there is a base difference between the normal and mutated DNA with the 3' terminus of the primer corresponding to the position in the sample where there is a difference between the normal and mutant, the primer being tagged or capable of being tagged, whereby the presence or absence of the tag in the PCR product is detected.

54. The method according to claim 51 in which a test sample is subjected to PCR with primers complementary to the normal target DNA wherein the primer for extending at the 3' end of the target anneals to a sequence the 3' nucleotide of which is

mutated in the mutant, the 3' primer bearing a tag or being capable of being tagged at or on the 3' nucleotide, wherein the presence of the tag in the PCR reaction product as detected.

55. The method according to claim 39 wherein said nucleic acid molecules are separated into linear and circular DNA molecules.

56. The method according to claim 55 further comprising introducing a tag to an end of the linear nucleic acid molecules, wherein said tag is capable of being immobilised on a matrix, by direct interaction with the matrix or by indirect interaction by means of a binding partner to the tag, and contacting the sample with a matrix or, where the tag interacts indirectly with the matrix, with the binding partner to the tag and with a matrix, whereby said tagged linear nucleic acid molecules are immobilised on the matrix.

57. The method according to claim 39 wherein said nucleic acid molecules are further subjected to in vitro packaging into bacteriophage particles.

58. The method according to claim 57 wherein a vector DNA is cut with one or more restriction enzymes, 3' OH groups of a vector DNA are blocked, vector and DNA to be inserted are contacted under conditions appropriate for ligation of DNA fragments, and the ligation products are tagged with a moiety capable of attaching to reactive 3' OH groups, followed by separation of tagged and untagged molecules.

59. A method of in vitro phage packaging of recombinant phage wherein a vector DNA is cut with one or more restriction enzymes, 3' OH groups of the vector DNA are blocked, vector and DNA to be inserted are contacted under conditions appropriate for ligation of DNA fragments, and the ligation products are tagged with a moiety capable of attaching to reactive 3' OH groups, followed by separation of tagged and untagged molecules.

60. A method of in vitro phage packaging of recombinant phage wherein a vector DNA is cut with one or more restriction enzymes, 3' OH groups of the vector DNA are blocked, vector and DNA to be inserted are contacted under conditions appropriate for ligation of DNA fragments, and a population of the ligation products is tagged with a moiety capable of attaching to reactive 3' OH groups, wherein the moiety is capable of being

immobilised on a matrix, the ligation products are contacted with a matrix, followed by separation of tagged and untagged molecules by the capturing of the tagged molecules by the matrix.

61. The method according to claim 60 wherein said population of ligation products is tagged with a moiety capable of being immobilised on a matrix either directly or indirectly via a binding partner for the tag, said method comprising contacting the ligation products with a matrix, or, where the tag interacts indirectly with the matrix by means of a binding partner, with a binding partner for the tag and with a matrix, whereby tagged molecules are captured by the matrix and thereby separated from untagged molecules.

62. A method of separating linear from circular nucleic acid molecules in a sample said method comprising introducing a tag to an end of a linear nucleic acid molecule, wherein said tag is capable of being immobilised on a matrix, by direct interaction with the matrix or by indirect interaction by means of a binding partner to the tag, and contacting the sample with a matrix or, where the tag interacts indirectly with the matrix, with the binding partner to the tag and with a matrix, whereby said tagged linear nucleic acid molecules are immobilised on the matrix.

63. The method according to claim 60 wherein the tag is a moiety which can be incorporated into a nucleic acid molecule or a moiety which has an affinity for a nucleic acid molecule.

64. The method according to claim 60 wherein the tag interacts directly with the matrix.

65. The method according to claim 60 wherein the tag interacts indirectly with the matrix by means of a binding partner for the tag.

66. The method according to claim 60 wherein the tag is a ligand.

67. The method according to claim 66 wherein the ligand is selected from biotin or fluorescein.

68. The method according to claim 60 wherein the tag is a steroid or a steroid like molecule.

69. The method according to claim 68 wherein the steroid is digoxygenin.

70. The method according to claim 60 wherein the tag is an antigen.

71. The method according to claim 60 wherein the tag is a protein.

72. The method according to claim 71 wherein the protein is a nucleic acid binding protein.

73. The method according to claim 60 wherein the tag is a nucleic acid molecule.

74. The method according to claim 60 wherein the tag is biotin, and the tag is captured by means of streptavidin or avidin.

75. The method according to claim 60 wherein the matrix is in the form of sheets, gels, filters, membranes, fibres, tubes, microtitre plates, columns, particles.

76. The method according to claim 75 wherein the matrix is a porous material.

77. The method according to claim 76 wherein the matrix is incorporated into a separation device selected from centrifuge vials, microtiter plates, cartridges and syringes.

78. The method according to claim 75 wherein an absorbent pad is located on said porous material, a liquid impermeable sheet is located on the face of said absorbent pad remote from said porous material, and a liquid impermeable sheet having one or more holes therein is located on the face of said porous material remote from said absorbent pad, whereby the test sample is applied to one of said holes and is caused to diffuse transversely through said porous material by absorption into said absorbent pad.

79. A method for constructing a gene library or a phage display library which comprises the use of a method as claimed in claim 59.

80. A method for at least partially separating nucleic acid molecules in a sample into populations wherein a population is tagged or capable of being tagged with a moiety capable of being immobilised on a matrix, said method comprising contacting the nucleic acid containing sample with a matrix whereby the tagged molecules are captured by the matrix and thereby separated from untagged molecules, wherein the matrix is in the form of sheets, gels, filters, membranes, fibres, tubes, microtitre plates, columns, particles, and wherein the matrix is a porous material, wherein an absorbent pad is located on said porous material, a liquid impermeable sheet is located on the face of said absorbent pad remote from said porous material, and a liquid impermeable sheet having one or more holes therein is located on the face of said porous material remote from said absorbent pad, whereby the test sample is applied to one of said holes and is caused to diffuse transversely through said porous material by absorption into said absorbent pad.

81. The method according to claim 80 wherein a population of molecules is tagged or capable of being tagged with a moiety capable of being immobilised on a matrix either directly or indirectly via a binding partner for the tag, said method comprising contacting the nucleic acid containing sample with a matrix, or, where the tag interacts indirectly with the matrix by means of a binding partner, with a binding partner for the tag and with a matrix, whereby tagged molecules are captured by the matrix and thereby separated from untagged molecules.

82. The method according to claim 80 wherein the tag is a moiety which can be incorporated into a nucleic acid molecule or a moiety which has an affinity for a nucleic acid molecule.

83. The method according to claim 80 wherein the tag interacts directly with the matrix.

84. The method according to claim 80 wherein the tag interacts indirectly with the matrix by means of a binding partner for the tag.

complementary to a region of the nucleic acid where there is a base difference between the normal and mutated DNA with the 3' terminus of the primer corresponding to the position in the sample where there is a difference between the normal and mutant, the primer being tagged or capable of being tagged, whereby the presence or absence of the tag in the PCR product is detected.

96. A method of diagnostic PCR in which a test sample is subjected to PCR with primers complementary to the normal target DNA wherein the primer for extending at the 3' end of the target anneals to a sequence the 3' nucleotide of which is mutated in the mutant, the 3' primer bearing a tag or being capable of being tagged at or on the 3' nucleotide, therein the presence of the tag in the PCR reaction product as detected.

REMARKS

Applicants respectfully request favorable consideration of the present application and claims. By this amendment, claims 39-96 have been added. The new claims are supported by the instant specification and thus, no new matter is added by this amendment. Early and favorable action by the Examiner is earnestly solicited.

Respectfully submitted,

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